

AD _____

Award Number: DAMD17-01-1-0080

TITLE: Epidermal Growth Factor (EGF) Receptor Intron 1 CA Repeat Polymorphisms in African-American and Caucasian Males: Influence on Prostate Cancer Risk or Disease Progression and Interaction with Androgen Receptor CAG Repeat Polymorphisms

PRINCIPAL INVESTIGATOR: David K. Moscatello, Ph.D.

CONTRACTING ORGANIZATION: Cornell Institute for Medical Research
Camden, New Jersey 08103

REPORT DATE: September 2005

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
<small>Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</small>					
1. REPORT DATE (DD-MM-YYYY) 01-09-2005		2. REPORT TYPE Final		3. DATES COVERED (From - To) 1 Sep 2001 – 31 Aug 2005	
4. TITLE AND SUBTITLE Epidermal Growth Factor (EGF) Receptor Intron 1 CA Repeat Polymorphisms in African-American and Caucasian Males: Influence on Prostate Cancer Risk or Disease...				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER DAMD17-01-1-0080	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) David K. Moscatello, Ph.D. E-Mail: dmoscate@coriell.umdj.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Cornell Institute for Medical Research Camden, New Jersey 08103				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT See next page					
15. SUBJECT TERMS Genetics and molecular biology; gene interactions/transcription; familial and hereditary carcinogenesis; polymorphism/research resources					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)
			UU	30	

ABSTRACT

We are investigating the effect of a polymorphic epidermal growth factor receptor (EGFR) gene intron 1 CA repeat on prostate cancer (CaP) development, alone or in combination with a known androgen receptor gene CAG repeat polymorphism. We will characterize these repeats in DNA from African-American and Caucasian men with CaP. The data will be analyzed for any correlation using both parameters with clinical outcome (age of onset, rapid progression, or metastasis). The Human Subjects Protocol was approved by the US Army MPMC HSRRB on 24 November 2003. However, the resignation of the study coordinator at the Cooper Hospital/University Medical Center last year and the failure of my clinical collaborator to train a new coordinator in a timely manner resulted in further delays in initiating subject recruitment. Fortunately, new clinical collaborators affiliated with Thomas Jefferson University (TJU) have agreed to participate in the study. This site has been approved by both the DOD and the HSRRB and has also approved the new Human Subjects Protocol. Subject recruitment at TJU was initiated in mid-February of this year. Since recruitment began, eighty-seven (87) new subjects entered the study, and we anticipate achieving our goal of 113 more (300 total) CaP subjects by mid-2007. A new urologist and study coordinator are now available at Cooper Hospital. We have requested a no-cost extension of the grant through June 2007 in order to complete the research.

Table of Contents

Table of Contents.....	4
Introduction.....	5
Body.....	5
Key Research Accomplishments.....	6
Reportable Outcomes.....	7
Conclusion.....	7
References.....	7
Appendices.....	9

INTRODUCTION: African-Americans are at increased risk of developing prostate cancer (CaP) relative to whites, and the lengths of two polymorphic repeats in the first exon of the androgen receptor (AR) gene contribute to that risk (Ries *et al*, 1990; Parker *et al*, 1996). The CAG repeat length is best correlated with prostate cancer risk, shorter repeats being associated with higher risk, and the prevalence of the shorter CAG alleles is greatest in African-American men, intermediate in Caucasian, and least in Asian-American men (Faber *et al*, 1989; Irvine *et al*, 1995; Kantoff *et al*, 1998; Pettaway, 1999). However, a multigenic etiology for CaP is likely. A polymorphic CA repeat has been described in intron 1 of the epidermal growth factor receptor (EGFR) gene, and the length of the repeat inversely correlated with transcriptional activity *in vitro* (Chi *et al*, 1992; Gebhardt *et al*, 1999). Preliminary evidence suggests that the CA repeat status affects EGFR content in breast cancer, and that shorter repeats might be a predisposing factor for breast cancer (Buerger *et al*, 2000). The EGFR is also important in regulation of prostatic epithelial and CaP cell growth, and androgen may affect that by increasing the levels of EGFR and its' ligands in CaP cells (Schuurmans *et al*, 1991; Liu *et al*, 1993). Shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, and potentially also by affecting alternative splicing of the EGFR transcript, could synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and promote the development of androgen-independent, metastatic prostate cancer. In collaboration with The Prostate Cancer Risk Assessment Program at Cooper Hospital/ University Medical Center and the Department of Urology at Thomas Jefferson University, we will isolate DNA from blood samples from 300 African-American and Caucasian American men with prostate cancer. We will determine the length of these two repeats, to determine whether the EGFR CA repeat, alone or in combination with the AR CAG repeat, affects CaP risk. Lymphoblastoid cell lines will be established for a representative subset of these samples, and will be made available to other researchers at the end of this study. The data will be analyzed for any correlation using both parameters with clinical outcome (age of onset, rapid progression, or metastasis).

BODY: Based on USAMRMC recommendation, a biostatistician, Dr. Constantine Daskalakis, was recruited to the study and a statistical analysis plan was developed. The present study (funded by award number DAMD17-01-1-0080) is considered to be a sub-study of the Regional Prostate Cancer Registry and Risk Assessment Program at Cooper Hospital/ University Medical Center by the Cooper Hospital/ University Medical Center IRB. Delays in granting of approval to commence research were caused by turnover of HSRRB reviewers working with the DOD (six different reviewers) and the implementation of the new HIPAA regulations by the Cooper Hospital/ University Medical Center Institutional Review. Approval to initiate my research was finally received from the US Army Medical Research and Materiel Command Human Subjects Research Review Board (USAMRMC HSRRB) in a letter dated 24 November 2003 (Modification No. P00001 to DAMD17-01-1-0080), three years after the initial grant award. Taking the long delay in obtaining HSRRB approval into account, the grant performance period was extended to 30 September 2005 (correspondence appended).

Unfortunately, shortly after receiving approval to initiate subject recruitment, the individual in Dr. Marmar's office who was to carry out the recruitment and specimen collection, Juliette May, resigned her position. This occurred in January of 2004. Being assured by Dr. Marmar that a new person would be hired soon, I acquired control cell lines and initiated laboratory work with these lines (see below). Evette Ortolaza was hired as Dr. Marmar's office manager, and was to begin subject recruitment for my project (CHS RP#02-046) upon completion of training in research with human subjects. However, several months passed without any indication that Ms. Ortolaza had received approval from the Cooper Health System IRB for participation in research involving human subjects, despite regular communications from me. These repeated delays by my clinical collaborator in the Cooper Health System have prevented enrollment of new study subjects, and if continued, would pose a problem for the successful completion of this research project. Therefore, I explored other avenues for subject enrollment, although I have kept the IRB protocol for the

study at Cooper active, inasmuch as 100 samples collected under a prior protocol are available through Cooper's Regional Prostate Cancer Registry. Fortunately, a new urologic surgeon has joined the Department of Urology at Cooper Health System, and we have received IRB approval for the addition of new Cooper investigators for subject recruitment, Dr. Justin D. Harmon and Monique S Wilson, APRN-BC will join the project to facilitate more rapid subject accrual.

Last year, I was able to report that Drs. Raffaele Baffa and Leonard Gomella of the Department of Urology at Thomas Jefferson University in Philadelphia agreed to participate in this research project. The Kimmel Cancer Center at Thomas Jefferson University is an NCI-Designated Cancer Center serving the greater Philadelphia area. Dr. Raffaele Baffa is Director of Urology Research, Department of Urology, and Co-Director of the Genito-Urinary Cancer Program at the Kimmel Cancer Center, and he thus works closely with Dr. Gomella. Dr. Baffa is a colleague I have known since 1993 when I was also at the Kimmel Cancer Center, and his interest in cancer genetics is longstanding (see appended curriculum vitae). Raffaele was instrumental in bringing Dr. Gomella on-board for the current research.

Dr. Gomella is Bernard W. Godwin, Jr., Professor of Prostate Cancer, Jefferson Medical College, Chairman of the Department of Urology, and Director of Urologic Oncology in the Kimmel Cancer Institute at Thomas Jefferson University. Dr. Gomella is expert in urologic oncology, with a long-standing interest in prostate cancer, as shown in his appended curriculum vitae. In addition to seeing patients and clinical work in support of basic research, he is principal investigator in a number of clinical trials. Of particular importance in the current context are his role in a longitudinal study to determine the utility of prostate-specific antigen (PSA) for early detection of prostate cancer, and in the placebo-controlled Selenium and Vitamin E Cancer Prevention Trial (SELECT A). He has been principal investigator in these studies since 1989 and 2001, respectively. He is also principle investigator in two prostate cancer treatment trials initiated in 2003. Thus, his office has a large pool of individuals already enrolled in clinical CaP studies, both with and without cancer. Importantly, this pool includes individuals with both metastatic and non-metastatic CaP diagnosed several years ago as well as recently. Since the focus of my study is on the role of specific inherited genetic polymorphisms in CaP, prior treatment of subjects will not interfere with the results. In combination with the regular patient pool, it is anticipated that this large pool of individuals who have already demonstrated a willingness to participate in research studies will facilitate the rapid accrual of subjects for the current study, since their opportunity cost for this study is minimal.

The clinical research coordinator in the Department of Urology, Ms. Christine Hubert, will enroll subjects. Ms. Hubert has acquired extensive experience as a clinical research coordinator in a variety of studies since 1997. Christine has been at Thomas Jefferson University since 1999, exclusively as Clinical study coordinator. This experience is outlined in her appended curriculum vitae, and Ms. Hubert has already proven her reliability by quickly arranging all the materials needed for approval of the study by the Jefferson Clinical Cancer Research Review Board (CCRRC).

Nevertheless, getting approvals through both the Clinical Cancer Research Review Board and the Institutional review Board at TJU required a substantial amount of time. The initial approval of the protocol by the IRB was not given until February 3, 2005, and unfortunately the approved consent did not include my name. The DOD HSRRB approved the addition of Thomas Jefferson University on April 19, 2005. Final approval of the amended consent by the Thomas Jefferson University Institutional Review Board was not obtained until May 18, 2005. The subcontract to pay the study coordinator was not approved by TJU until the end of 2005, and subject recruitment at TJU was initiated in February 2006. Since enrollment of new subjects was initiated, 87 new subjects have joined the study, bringing the total available to 199 (including samples accrued in a prior protocol). The 2006 Human subjects approval documents from TJU are appended.

KEY RESEARCH ACCOMPLISHMENTS: New clinical collaborators at an NCI-designated Cancer Center have agreed to participate in subject recruitment (Task 1a). This is key to enrolling sufficient subjects for

successful completion of the study. Control cell lines have been acquired and grown, and DNA has been isolated from these lines. We have determined the androgen receptor CAG repeat sizes by fragment size analysis in small panels available in-house. And we have begun analysis of both repeat polymorphisms in 200 "apparently normal" controls from two pre-existing Coriell panels (100 Caucasians and 100 African Americans). We have not yet accrued sufficient new subjects for statistically significant analyses.

REPORTABLE OUTCOMES: We have initiated subject recruitment from the new collection site, and are analyzing DNA samples from control samples in the Coriell Cell Repositories. We have not yet accrued sufficient cases to carry out any meaningful statistical analysis.

CONCLUSIONS: Despite tremendous progress in research into the origins of prostate cancer (CaP), there are still many important, unresolved questions about the etiology of this common cancer. Perhaps the most urgent problem facing prostate cancer researchers -- and those with the disease -- is to identify the subset of CaP sufferers whose cancer will progress rapidly. Despite extensive research, no single marker has arisen as a definitive marker of such cancers. Indeed, a multigenic etiology for CaP is extremely likely. Among the candidate genes are those encoding the androgen receptor and the epidermal growth factor receptor (EGFR). The EGFR is clearly important in the regulation of prostatic epithelial and CaP cell growth, and is frequently overexpressed in BPH and CaP cells, but no studies have convincingly demonstrated that it is of great use in predicting the course of a particular CaP case. However, a polymorphic CA repeat has been described in intron 1 of the epidermal growth factor receptor (EGFR) gene, and the length of the repeat has recently been inversely correlated with transcriptional activity *in vitro* (Chi *et al*, 1992; Gebhardt *et al*, 1999). Androgen may also influence the expression of the EGFR by increasing the levels of its' ligands, and perhaps directly in CaP cells (Schuurmans *et al*, 1991; Liu *et al*, 1993). However, the possible contribution of EGFR CA repeat polymorphisms on prostate cancer risk or progression has never been investigated. Shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, and potentially also by affecting alternative splicing of the EGFR transcript, could synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and promote the development of androgen-independent, metastatic prostate cancer. No work addressing these issues with respect to CaP has been published to date, although Buerger *et al* recently reported (2004) new results associating the allelic length of the EGFR CA repeat with EGFR gene amplification in breast cancers. This proposal will address these possibilities, and will also provide resources for definitive future studies.

Given our current pace of subject recruitment and additional personnel, we anticipate expeditious recruitment of the research subjects now that the subcontract has been approved.

It is important to emphasize that subject recruitment is the limiting factor in this research. The mononuclear cell isolation, DNA extraction, and polymerase chain reaction (PCR) analyses are standard techniques with which the investigators have extensive experience, and large numbers of samples can be analyzed in a short period of time.

We have thus respectfully requested a no-cost extension of the grant through June 2007 in order to complete the research. Given that the initial DOD HSRRB approval to initiate the project was given at the end of 2003, please note that this extension will functionally constitute a 7-month extension of the originally proposed three-year project.

BACKGROUND REFERENCES:

Buerger, H, Packeisen, J, Boecker, A, Tidow, N, Kersting, C, Bielawski, K, J Isola, J, Yatabe, Y, Nakachi, K, Boecker, W, and Brandt, B. (2004) Allelic length of a CA dinucleotide repeat in the *egfr* gene correlates

with the frequency of amplifications of this sequence—first results of an inter-ethnic breast cancer study. *J Pathol*, 203(1): 545-50.

Buerger, H., Gebhardt, F., Schmidt, H., Beckmann, A., Hutmacher, K., Simon, R., Lelle, R., Boeker, W., and Brandt, B. (2000) Length and loss of heterozygosity of an intron 1 polymorphic sequence of EGFR is related to cytogenetic alterations and epithelial growth factor receptor expression. *Cancer Research* 60, 854-857.

Chi, D.D., Hing, A.V., Helms, C., Steinbrueck, T., Mishra, S.K., and Donis-Keller, H. (1992) Two chromosome 7 dinucleotide repeat polymorphisms at gene loci epidermal growth factor receptor (EGFR) and pro alpha 2 (I) collagen (COL1A2). *Hum. Mol. Gen.* 1, 135.

Faber, P.W., Kuiper, G.G., van Rooij, H.C., van der Korput, J.A., Brinkmann, A.O., and Trapman, J. (1989) The N-terminal domain of the human androgen receptor is encoded by one, large exon. *Mol. Cell. Endocrinol.* 61, 257-162.

Gebhardt, F., Zanker, K.S., and Brandt, B. (1999) Modulation of epidermal growth factor receptor gene transcription by a polymorphic dinucleotide repeat in intron 1. *J. Biol. Chem.* 274, 13176-13180.

Irvine, R.A., Yu, M.C., Ross, R.K., and Coetzee, G.A. (1995) The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. *Cancer Res.* 55, 1937-1940.

Kantoff, P., Giovannucci, E., and Brown M. (1998) The androgen receptor CAG repeat polymorphism and its relationship to prostate cancer. *Biochimica et Biophysica Acta.* 1378:C1-5.

Liu, X.H., Wiley, H.S., and Meikle, A.W. (1993) Androgens regulate proliferation of human prostate cancer cells in culture by increasing transforming growth factor-alpha (TGF-alpha) and epidermal growth factor (EGF)/TGF-alpha receptor. *J. Clin. Endocrinol. Metab.* 77, 1472-1478.

Parker, S.L., Tong, T., Bolden, S., and Wingo, P.A. (1996) Cancer statistics, 1996. *CA Cancer J. Clin.* 65, 5-27.

Pettaway, C.A. (1999) Racial differences in the androgen/androgen receptor pathway in prostate cancer. *J. Natl. Med. Assoc.* 91, 653-60.

Ries, L.A.G., Hankey, B.F., and Edwards, B.K. Cancer Statistics Review 1973-1987. (1990) United States Public Health Service, NIH publication No. 90-2799, Bethesda, MD.

Schuurmans, A.L., Bolt, J., Veldscholte, J., and Mulder E. (1990) Stimulatory effects of antiandrogens on LNCaP human prostate tumor cell growth, EGF-receptor level and acid phosphatase secretion. *J. Ster. Biochem. Mol. Biol.* 37, 849-853.

HSRRB Log No. A-10414/ PC001407 - " Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat polymorphisms in African-American and Caucasian males: Influence on Prostate Cancer risk or disease progression and interaction with Androgen receptor CAG repeat polymorphisms."

Human Subjects Protocol

1. This grant will utilize specimens and information accrued through The Prostate Cancer Risk Assessment Program, a collaborative project of Cooper Hospital/ University Medical Center and The Coriell Institute for Medical Research. The overall study is entitled "Development of a regional prostate cancer registry & risk assessment program".
2. This protocol does NOT involve the testing of Investigational New Drugs or Devices.
3. Principal Investigator (PC001407):

David K. Moscatello, Ph.D.
Coriell Institute for Medical Research
403 Haddon Avenue
Camden, New Jersey 08103
(856) 966-5054
dmoscate@cimr.umdj.edu

Principal Investigators (Regional Prostate Cancer Registry and Risk Assessment Program):

Dr. Justin D. Harmon, D.O.
Department of Surgery
Division of Urology
Three Cooper Plaza, Suite 403
Camden, New Jersey 08103
(856) 963-3577
harmon-justin@cooperhealth.edu

Generosa Grana, M.D.
Hematology/ Oncology
Three Cooper Plaza, Suite 215
Camden, New Jersey 08103
(856) 342-2439
Grana-Generosa@cooperhealth.edu

Principal Investigators (Kimmel Cancer Institute, Thomas Jefferson University)

Leonard Gomella, M.D.
Director, Urologic Oncology
& Chairman, Dept. of Urology
Department of Urology
Kimmel Cancer Center
Thomas Jefferson University
1025 Walnut Street
Philadelphia, PA 19107
Phone: (215) 955-1702
Fax: (215) 923-1884
leonard.gomella@mail.tju.edu

Raffaele Baffa, M.D.
Director of Urology Research
& Co-Director Genito-Urinary Cancer Program
Department of Urology
Kimmel Cancer Center
Thomas Jefferson University
1025 Walnut Street, Suite 1102A
Philadelphia, PA 19107
Phone: (215) 955-9072
Fax: (215) 923-1884
raffaele.baffa@jefferson.edu

Christine D. Hubert
Clinical Study Coordinator

Thomas Jefferson University
Department of Urology
Room 1100 College
1025 Walnut Street
Philadelphia, PA 19107
Phone: (215) 955-4202
christine.hubert@jefferson.edu

4. Location of Study: Cooper Hospital/ University Medical Center
One Cooper Plaza
Camden, New Jersey 08103-1489
(856) 342-2000

Coriell Institute for Medical Research
403 Haddon Avenue
Camden, New Jersey 08103
(856) 966-7377

Thomas Jefferson University
Department of Urology
1025 Walnut Street, Suite 1102A
Philadelphia, PA 19107
(215) 955-1702

5. Time required to complete: Expected Start: 24 November, 2003
Completion: 31 September, 2006

6 - 9. Protocol

a. Research Hypotheses/ Objectives: This study involves the development of a prostate cancer database that will collect data not currently available on prostate cancer patients and their family members. Personal information and blood samples will be collected from all participants, and tissue samples will be collected from participants that undergo medically indicated biopsies or surgeries. Regarding PC001407, I hypothesize that shorter CA repeats in intron 1 of the EGFR gene, by resulting in transcriptional enhancement of EGF receptor expression, will synergize with shorter CAG androgen receptor AR repeats to increase the risk of early onset prostate cancer and/ or promote the development of androgen-independent, aggressive prostate cancer. The status of Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat and androgen receptor CAG repeat polymorphisms in African-American and Caucasian males will be determined by PCR analysis of DNA isolated from blood samples. These data will be studied in conjunction with the personal and medical information to determine whether the status of the EGF receptor polymorphism, alone or in combination with the androgen receptor polymorphism, influences the age of onset or biological characteristics (e.g., hormone dependence, invasiveness, metastasis) of prostate cancer. Further details are described in the included abstract.

b. Study Population: The study population will be comprised of approximately 300 males recruited from individuals who come to the Department of Urology at Thomas Jefferson University for prostate cancer treatment or screening, and to Cooper Hospital for the treatment of prostate cancer and via the Prostate Cancer Risk Assessment Program at Cooper Hospital. Cooper Hospital serves primarily Camden County

and western Burlington County, New Jersey, and ethnically diverse area with significant African-American, Caucasian, and Hispanic populations.

- c. Inclusion and Exclusion Criteria: All subjects recruited will be males in the age range of 35 - 69 years. Carcinoma of the prostate (CaP) is rare among individuals under age 35, whereas prostatic intraepithelial neoplasia (PIN) the presumed precursor of CaP, is very common among men older than 70, so older individuals are less likely to be informative regarding hereditary predisposition. Because the frequency of the various EGF receptor intron 1 CA repeat lengths in African-American men is currently unknown, and since African-American men are at greater risk of prostate cancer than the general population, we will recruit a significant fraction of subjects from the African-American community. Subjects accrued to date under the previously approved Prostate Cancer Risk Assessment Program protocol are ca. 50% African-American and 50% Caucasian.
- d. Informed Consent Process: The Clinical Study Coordinator in the Department of Urology at Thomas Jefferson University or Clinical nursing staff at Cooper Hospital/University Medical Center will explain The Prostate Cancer Risk Assessment Program in lay terms to prospective subjects who come to the weekly screening clinic ("self-recruitment"). The Prostate Cancer Risk Assessment Program is open to men between the ages of 35 and 69 who are African-American, or of any race with a family history of prostate cancer. Prostate cancer patients of Dr. Justin Harmon will also be offered the opportunity to enroll in the study. Individuals uncertain about participation may discuss the study with friends and family members and return at a later time. Interested individuals will then be talked through the informed consent form (appended), with particular attention being focussed on the clauses regarding (a) the choice to be informed of any clinical implications of their results in the context of this or other relevant prostate cancer studies, (b) the risks of participation in the study, and (c) sample donation. Witnesses may be other clinic personnel or any other individual the subjects choose. As the document is discussed, the subjects and their witnesses will be asked to initial each page to indicate that it has been explained to them, as well as to sign the last page of the document to indicate their agreement to participate in the study. Two copies of the consent form will be completed so that the subjects can keep an original copy.
- e. Sample Size: A target of 300 individuals will be sought over the course of 3 years. (The overall target for the Regional Prostate Cancer Registry and Risk Assessment Program is 400 subjects, but the time and funds for PC001407 will allow for analysis of 300.) By recommendation of peer review, a biostatistician has been consulted regarding sample size (appended), and will be consulted for subsequent data analyses. EGFR intron 1 CA repeat allele frequencies in the general populations of African-American and Caucasian American men will be determined by analysis of DNA samples from apparently normal individuals in existing Coriell Cell Repository panels.
- f. Protocol Design: Male subjects (300) will be recruited from individuals who come for screening or treatment of prostate cancer and via the Prostate Cancer Risk Assessment Program at Cooper Hospital as described in b - d above. Notices will be published as in the appended Cooper Health system newsletter. After informed consent is obtained as described in (d), subjects will be asked to complete a Health History Questionnaire (appended), and to donate 3 (~10 ml each) tubes of blood. One tube will be used by the hospital for medical diagnosis (e.g., Prostate Specific Antigen level), while the other tubes will be used at the Coriell Institute for Medical Research for (a) extraction of DNA and (b) isolation and cryopreservation of lymphocytes. Blood will be collected no more than once per year for the purposes of this study. The lengths of the EGFR intron 1 CA repeat and the AR CAG repeat will be determined by PCR analysis of the DNA (of the samples accrued to date on a previous protocol, the AR repeat has already been analyzed in several dozen). Epstein-Barr virus-immortalized lymphoblastoid cell lines will be established for individuals representing the possible combinations of these two polymorphisms. These cell lines will be deposited in the

National Institute of Aging Repository in the Coriell Cell Repositories, and will be available to other researchers at the end of this study. We will also utilize prostate biopsies, when obtained as part of the subjects' medical care, to examine EGFR and AR expression and initiate prostate cell lines. The specimens, health histories, and clinical information will be encoded as PS### (e.g., PS100, PS101, etc.) by the Cooper Hospital clinical staff, such that all specimens and information received by The Coriell Institute for Medical Research will be separated from subject names. Coriell will receive only coded summaries of the Health History Questionnaires. Any cell lines accepted by the Coriell Cell Repositories for distribution to other researchers will be given new code numbers (e.g., AG00000) to ensure confidentiality. For PS### cell lines to be submitted to the Coriell Cell Repositories, Dr. Justin Harmon's clinical staff will assign new numbers from a list of the next available AG numbers; the list indicating the PS #s corresponding to the new AG numbers will be kept by his office for 4 years after completion of the study.

g. Risks to Subjects: As this is not an interventional protocol, this project poses no greater than minimal risk to participants. Risks noted in the consent form include the risk of discovering a genetic predisposition to cancer, which may cause concern. Subjects may also have concerns even if they are not in the future told that they have a gene alteration that has been linked to an increased risk of prostate cancer. Subjects do not have to agree to have this information revealed to them or their family members. The risks and discomfort associated with giving blood include the possibility of bleeding and bruising. This rarely causes a significant problem.

h. Benefits to Subjects: As noted in the consent form, subjects will not receive any immediate benefits as a result of participation in this study. It is possible that the study will reveal known or novel genetic polymorphisms that would indicate a statistically greater or lesser prostate cancer risk than the general population. This might prompt an individual to have regular screening for prostate cancer, which could affect their prognosis should cancer be discovered. However, such information is more likely to be of use in the future, rather than to subjects recruited in the current study.

i. Roles and Responsibilities of Study Personnel: Local review boards have not found the protocol to be of greater than minimal risk, so no medical monitor has been assigned.

David K. Moscatello, Ph.D. Role: Principal Investigator (PC001407), 40%. Lymphocyte and DNA isolation, analysis of EGFR intron 1 CA repeats, analysis of Androgen receptor CAG repeats, preparation of DNA, RNA, and protein lysates from prostate specimens, immunohistochemistry and western blotting, reverse transcription-polymerase chain reaction (RT-PCR), Southern and Northern blotting, cryopreservation of viable prostate biopsies, and data analysis.

Bender, Patrick K., Ph.D. (Associate Professor and Supervisor, Division of Molecular Biology, Coriell Institute for Medical Research, 5%. Role: Analysis of Androgen Receptor CAG repeats.

Leonard Gomella, M.D., (Professor of Urology, Director, Urologic Oncology & Chairman, Dept. of Urology, Kimmel Cancer Center, Thomas Jefferson University. Role: subject recruitment.

Raffaele Baffa, M.D. (Associate Professor, Director of Urology Research and Co-Director Genito-Urinary Cancer Program, Department of Urology, Kimmel Cancer Center, Thomas Jefferson University). Role: subject recruitment.

Christine Hubert, B.A. (Clinical Study Coordinator, Department of Urology, Thomas Jefferson University). Role: subject recruitment, interviews, data entry and encoding.

Grana, Generosa, M.D., Assistant Professor of Hematology/ Oncology and Medical Director, The Cancer Risk Evaluation Center, Cooper Hospital/University Medical Center, 5%. Role: Medical Director, The Cancer Risk Evaluation Center.

Harmon, Justin D., D.O., Department of Surgery, Division of Urology, Cooper Hospital/ University Medical Center, 5%. Role: Procurement of benign and malignant prostate specimens.

Milagro Concepcion, B.A., Technician, Coriell Institute for Medical Research, 50%. Role: Lymphocyte isolation and cryopreservation, DNA isolation, and PCR.

Constantine Daskalakis, Sc.D., Biostatistics section of the Department of Medicine, Thomas Jefferson University, Philadelphia, PA, 5%. Role: Consultant for study design and data analyses.

10. Reporting of serious and unexpected adverse events. This is not an IND or IDE protocol. No medical interventions are proposed. However, there is a remote possibility of a severe adverse event such as excessive bleeding or infection as a result of blood collection. Should such an event occur, Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy for Regulatory Compliance and Quality (301-619-2165) and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days.

11. Description of Protocol Drug(s) or Device(s): Not applicable.

12. Disposition of data: All health history and clinical records will be maintained at Thomas Jefferson University Hospital or Cooper Hospital/ University Medical Center according to their standard procedures. No disposal is contemplated, except for individuals who are withdrawn from the study (either voluntarily or otherwise), in which case the health questionnaires held at Cooper, and samples and associated data held at Coriell will be destroyed. Otherwise, encoded/ tabulated data without personal identifiers of just the subset of samples that will be submitted to the NIA Cell Repository will be maintained in the secure files of The Coriell Institute for Medical Research indefinitely.

13. Modification of the protocol: As this is not an IND/ IDE protocol, no modifications are anticipated, with the possible exception of the recruitment of additional subjects. This might be necessary to achieve statistical validity of possible correlations between the genetic polymorphisms and clinical data. The use of additional methods to recruit subjects might be considered if targets are not met. If this becomes necessary, the revisions, including any proposed new recruiting methods, will be submitted to the Institutional Review Boards of both local institutions, and subsequently to the OTSG HSRRB for approval.

14. Departure from the Protocol: Any departures from the proposed protocol with respect to the consents, questionnaires, or specimens will be submitted to the Institutional Review Boards of both local institutions, and subsequently to the OTSG HSRRB.
15. Roles and Responsibilities of Study Personnel: See (i) above.
16. USAMRMC Volunteer Registry Database: Project judged not greater than minimal risk by local review boards, therefore not applicable.

Signature of Principal Investigator: _____
David K. Moscatello, Ph.D.

Date: _____

STATISTICAL ANALYSIS PLAN

Our analyses will be based on samples obtained from 300 prostate cancer patients (prospectively collected) and from approximately 200 controls (from existing panels). The study's aims are to evaluate

- (1) the association between EGFR intron 1 CA repeats and prostate cancer;
- (2) the association between AR CAG repeats and prostate cancer; and
- (3) the combined (synergistic) effect of EGFR and AR on prostate cancer.

The first two aims pertain to the main effect of each gene, while the third aim focuses on their possible interaction. Preliminary analyses will be based on two-by-two cross-classification tables of each gene with prostate cancer status (case/control). We will estimate and test the (crude) unadjusted odds ratio separately for each gene, using Fisher's exact test and Mantel-Haenszel stratification analysis. We will then model the outcome (prostate cancer case or control status) as a function of both genes via logistic regression. In this multivariable analysis, we will also control for age, race, and other potential confounders.

Finally, we will test the hypotheses of "no multiplicative interaction" and "no additive interaction" between the two genes. Using the long-EGFR/long-AR combination as the referent group, the hypothesis of no multiplicative interaction implies that the joint odds ratio for the short-EGFR/short-AR combination is equal to the product of the two main effects odds ratio (i.e., short-EGFR/long-AR and long-EGFR/short-AR). The test of this hypothesis involves testing the product interaction term; likelihood ratio and Wald tests are straightforward to compute in all statistical packages. The hypothesis of no additive interaction, on the other hand, implies that the joint odds ratio is the sum of the two main effects odds ratios minus one. Although preprogrammed software capabilities do not allow testing of this hypothesis in logistic regression, we have a SAS macro that will allow us to perform the corresponding likelihood ratio and Wald tests.

We have also planned secondary analyses to assess:

1. the effects of the two genes among Caucasian and African-American subjects (i.e., gene-by-race interactions); and
2. the association between the length of the repeats for each gene and cancer recurrence and/or survival (among the prostate cancer cases only).

SAMPLE SIZE AND POWER

Based on previous data, EGFR intron 1 CA repeats show a distribution with 3 peaks in the general population, at 20, 18 and 16 repeats. A smaller number of repeats (<17, approximately 45% in the general population) are hypothesized to be associated with higher risk of prostate cancer. With 300 cases and 200 controls, using a two-tailed Fisher's exact test with alpha of 0.05, we have 84% power to detect an odds ratio of about 1.75 (i.e., short allele in 45% of the controls vs. 59% of the cases).

Similarly, based on previous data, AR CAG short repeats (<20) seem to be present in about 30% of the general population. With 300 cases and 200 controls, using a two-tailed Fisher's exact test with alpha of 0.05, we have 82% power to detect an odds ratio of 1.75 (i.e., short allele in 30% of the controls vs. 43% of the cases).

In terms of the interaction between the two genes, we have good power to detect moderate interactions on both the additive and the multiplicative scale. All power calculations were performed via Monte-Carlo simulation, using the appropriate likelihood ratio tests in logistic regression, with alpha of 0.05.

Assuming main effect odds ratios for each gene of about 1.75, under the "no additive interaction hypothesis", we expect a joint odds ratio of 2.5 (i.e., $1.75 + 1.75 - 1$) for the comparison of the short-EGFR/short-AR combination with the referent long-EGFR/long-AR combination. In our study, we have power to detect

departures from additivity when the synergy factor is 3 or higher (i.e., an odds ratio for the joint effect of 5.5 or higher):

Allele EGFR	AR	Effect type	OR	OR	Power	OR	Power
long	long	refer.	1.00				
long	short	main	1.75				
short	long	main	1.75				
short	short	joint	2.50*	5.5	81%	6.5	91%

(*) Additivity of effect (i.e., no additive interaction)

With the same assumptions of main effect odds ratios for each gene of about 1.75, under the "no multiplicative interaction hypothesis", we expect an odds ratio of 3.06 (i.e., 1.75×1.75) for the comparison of the short-EGFR/short-AR combination with the referent long-EGFR/long-AR combination. In our study, we have power to detect a multiplicative interaction factor of about 3 or higher (i.e., an odds ratio for the joint effect of 9 or higher):

Allele EGFR	AR	Effect type	OR	OR	Power	OR	Power
long	long	refer.	1.00				
long	short	main	1.75				
short	long	main	1.75				
short	short	joint	3.06*	9.2	75%	10.7	85%

(*) Multiplicativity of effect (i.e., no multiplicative interaction)

Constantine Daskalakis, ScD

Assistant Professor,

Biostatistics Section, Thomas Jefferson University,

125 S. 9th St. #402, Philadelphia, PA 19107

Tel: 215-955-5695

Fax: 215-503-3804

Email: constantine.daskalakis@mail.tju.edu

Moscatello, David K.

Subject: FW: A-10414.b, Approval Memo (Proposal Log Number PC001407, Award Number DAMD17-01-1-0080)

Date: Tue, 19 Apr 2005 07:50:25 -0400

X-MS-Has-Attach: yes

X-MS-TNEF-Correlator:

Thread-Topic: A-10414.b, Approval Memo (Proposal Log Number PC001407, Award Number DAMD17-01-1-0080)

Thread-Index: AcVEXoVxatQDbGm3QX+SYMHrIusQwAdmsPg

From: "Tuzson, Tibor Mr USAMRMC" <Tiberu.Tuzson@det.amedd.army.mil>

To: "David K. Moscatello" <dmoscate@coriell.org>

X-OriginalArrivalTime: 19 Apr 2005 11:50:26.0107 (UTC) FILETIME=[F9E340B0:01C544D5]

Dear Dr. Moscatello,

Below please find for your information, the notification of HSRRB approval of the Thomas Jefferson University study site that has been sent to the Contract Specialist. The Contract Specialist will send you notification of approval/modification to the grant. Please don't hesitate to contact me with any questions.

Best regards,
Tibor

Tibor Tuzson
Human Subjects Protection Scientist
U.S. Army Medical Research and Materiel Command
Phone: 301-619-6192
Fax: 301-619-7803

From: Brosch, Laura R COL USAMRMC

Sent: Monday, April 18, 2005 5:35 PM

To: Cardwell, Archie B Mr USAMRAA

Cc: Mishra, Nrusingha C Dr USAMRMC; Brosch, Laura R COL USAMRMC; Duchesneau, Caryn L Ms USAMRMC; Bennett, Jodi H Ms USAMRMC; Tuzson, Tibor Mr USAMRMC

Subject: A-10414.b, Approval Memo (Proposal Log Number PC001407, Award Number DAMD17-01-1-0080)

SUBJECT: Approval of Addition of Site to Protocol, "Epidermal Growth Factor (EGF) Receptor Intron 1 CA Repeat Polymorphisms in African-American and Caucasian Males: Influence on Prostate Cancer Risk or Disease Progression and Interaction with Androgen Receptor CAG Repeat Polymorphisms," Submitted by David K. Moscatello, Ph.D., Coriell Institute for Medical Research, Camden, New Jersey, (Site Principal Investigator: Raffaele Baffa, M.D., Thomas Jefferson University Hospital, Philadelphia, Pennsylvania), Proposal Log Number PC001407, Award Number DAMD17-01-1-0080, HSRRB Log Number A-10414 b

1. The related study documents regarding addition of the study site at Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, most recently received on 22 March 2005, have been reviewed and found to comply with applicable human subjects protection regulations. Documentation of the Thomas Jefferson University Hospital Institutional Review Board (IRB) approval of the protocol and consent form (version dated approved on 16 March 2005), was also received on 22 March 2005.
2. There are no outstanding human subjects protection issues to be resolved. This minimal risk protocol is approved for implementation at Thomas Jefferson University Hospital study site. Separate approval will be required prior to implementation at additional study sites.
3. The Use of Human Subjects Clause and the Use of Human Anatomical Substances Clause should be entered into the Assistance Agreement for the Thomas Jefferson University Hospital study site.

4. Submission of the Volunteer Registry Data Sheet is not required for this study.
5. Any protocol modifications (including but not limited to changes in the principal investigator, inclusion/exclusion criteria, number of subjects to be enrolled, study sites, or procedures) must be submitted as a written amendment for HSRRB acceptance. Documentation that the local IRB reviewed and approved the modifications must also be submitted.
6. In accordance with 32 Code of Federal Regulations 219, a continuing review report must be submitted to the local Institutional Review Board. According to our records, the continuing review report is due to the Thomas Jefferson University Hospital IRB on or before 26 January 2006. A copy of the continuing review report and the Thomas Jefferson University Hospital IRB approval of that report, is to be forwarded to the Acting Chair, HSRRB, as soon as possible after local approval is obtained.
7. Point of contact for this action is Mr. Tibor Tuzson at 301-619-6192.

LAURA R. BROSCH, PhD
COL, AN
Acting Chair, Human Subjects Research Review Board

02/02/2006 11:31 2159231884

TJU UROLOGY

PAGE 02/11



Thomas
Jefferson
University

Office of Scientific Affairs
Division of Human Subjects Protection
Institutional Review Board

January 18, 2006

BEST AVAILABLE COPY

Founded 1824

Jefferson Medical
College

Jefferson College of
Graduate Studies

Jefferson College of
Health Professions

Jefferson University
Physicians

Raffaele Baffa, MD
Urology & Coriell Institute
College, 11th Floor

Dear Dr. Baffa:

The Institutional Review Board (IRB) has reviewed the involvement of humans as research subjects in your study entitled:

"Epidermal Growth Factor (EGF) Receptor Intron 1 CA Repeat Polymorphisms in African-American and Caucasian Males: Influence on Prostate Cancer Risk or Disease Progression and Interaction With Androgen Receptor CAG Repeat Polymorphisms" (DOD) Control #05C.36

In accordance with Federal Wide Assurance (FWA) # 00002109 to the U.S. Department of Health and Human Services and per 45 CFR 46.110, Item (2)(a) Blood Draw & (7) Questionnaire, this continuing review was given expedited administrative approval on 1/10/06. Board #152 was notified at its 1/12/06 meeting.

☒ EXPEDITED (Continuing Review) ☐ FULL BOARD Review.

THIS APPROVAL REQUIRES THAT INFORMED CONSENT BE OBTAINED FROM ALL PERSONS PRIOR TO THEIR INVOLVEMENT IN THE STUDY BY USE OF THE LATEST, APPROVED, STAMPED CONSENT FORM.

Each subject must receive a copy of the stamped, signed consent form.

This approval expires on 1/9/07, one year from the approval date specified above, unless suspended or terminated earlier by action of the IRB. At the end of the current approval, a report (Form OSA-9) must be submitted to the IRB summarizing progress on the study during that period.

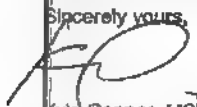
If you wish to continue the study beyond the expiration of this approval, an application for continuation of your study must be submitted to the IRB.

Any injury and/or unanticipated problem involving risks to the human research subjects not included in the written consent form must be reported promptly to the IRB using Form OSA-10 OFF-SITE or OSA-10 ON-SITE. This report should describe the event, evaluate its probable relationship to the experimental treatment received by the subject, and summarize the resulting outcome of the event.

Any proposed change in the protocol or in the written consent form must be submitted to the IRB for review and approval using Form OSA-12 before the proposed change can be implemented.

This approval verifies that the IRB operates in accordance with applicable ICH, national, local and institutional regulations.

Sincerely yours,


Kyle Connor, MS, CIP
Assistant Director
Division of Human Subjects Protection

KCI/r

02/02/2006 11:31 2159231884

TJU UROLOGY

PAGE 03/11

OSA-8
6/04Thomas Jefferson University
Raffaele Raffa, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #05C36
DOD/Coriell Institute
Page 1 of 8Thomas Jefferson University
Informed Consent Document for Human Subjects ResearchDepartment: Urology and The Coriell Institute for Medical Research (Dr. Moscatello)Principal Investigator: Raffaele Raffa, MD Telephone: 215-955-6961Co-Investigator(s): Leonard Gomella, MD; Edonard Trabulsi, MD; Deborah Glassman, MD;
David Moscatello, PhDTelephone: 215-955-6961Medical Title: Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat
polymorphisms in African-American and Caucasian males: Influence on Prostate Cancer risk or
disease progression and interaction with Androgen receptor CAG repeat polymorphisms.Lay Title: Testing patients with prostate cancer to see if they have genetic factors that might
influence their cancer risk or cancer progression

What Is an Informed Consent?

You are being asked to take part in a medical research study. Before you can make a knowledgeable decision about whether to participate, you should understand the possible risks and benefits related to this study. This process of learning and thinking about a study before you make a decision is known as *informed consent* and includes:

- Receiving detailed information about this research study;
- Being asked to read, sign and date this consent form, once you understand the study and have decided to participate. If you don't understand something about the study or if you have questions, you should ask for an explanation before you sign this form;
- Being given a copy of your signed and dated consent form to keep for your own records.

You should understand that your relationship with the study doctor is different than your relationship with your family doctor. Your family doctor treats your specific health problem with

Subject Initials: _____

Date: _____

Do Not Write Below This Line

For IRB Stamping

Thomas Jefferson University IRB
Approval Date 1-10-06
Expiration Date 1-9-07
Annual review due 6 weeks before expiration.

Thomas Jefferson University
Raffaello Baffa, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #05C.36
DOD/Coriell Institute
Page 2 of 8

the goal of making you better. The study doctor treats all subjects according to a research plan to obtain information about the experimental drug, device or procedure being studied and with the understanding that you may or may not benefit from your participation in the study. You should ask questions of the study doctor if you want to know more about this.

Introduction and Study Purpose

The Department of Urology is currently conducting a research study on the causes of Prostate cancer to find new methods of prevention, diagnosis and treatment. Before you make any decision to become involved, it is important that you read the following explanation. It describes the purpose of the study, what procedures will take place, and the benefits, risks and discomforts, and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time.

You are invited to participate in this research study because 1) You have been diagnosed with prostate cancer or 2) You do not have a prior history or clinical evidence of prostate cancer (control group-which is a group of patients that serves as the basis of comparison). This study will involve the development of a prostate cancer database that will collect data not currently available on prostate cancer patients and their family members. Personal information and blood samples will be collected from participants. Researchers, including scientists at Coriell Institute for Medical Research, who would like to study possible causes of cancer such as genes, lifestyles and environmental factors will use the samples and information.

It is estimated that 100 participants a year and approximately 300 participants over a 3 year period will be enrolled in this study at Thomas Jefferson University. It is estimated that a total of 300 participants will be enrolled at Thomas Jefferson University. You will be enrolled in the study for up to 3 years.

Procedures/Treatment

In addition to your routine care, blood samples will be drawn. Each participant will also be asked to provide lifestyle, medical and family history information. Specifically we will ask you to do the following:

1. Complete a questionnaire on your family history of cancer, as well as medical and lifestyle information. You may refuse to answer any question on the questionnaire that makes you uncomfortable.
2. Donate two tubes of blood (about 2 tablespoons) that will be drawn from a vein in your arm. You may be asked to donate blood samples periodically throughout the study, but no more than once per year.

Subject Initials: _____

Date: _____

Thomas Jefferson University
Raffaele Boffa, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #05C36
DOD/Coriell Institute
Page 3 of 8

3. Complete a follow-up questionnaire each year for four years to update the registry files on your health and to reconfirm your willingness to participate in the study. (Subjects who enroll on the 2nd year will receive 1 year follow-up.)

The methods used in this study are investigational, and we are not sure of the meaning of the results. It is possible that you will be discovered to have a gene that may be linked to an increased risk of developing a more aggressive form of prostate cancer. It is your option to be told or not told this information.

You are being asked to make that choice in this form by checking the box next to the "Yes" or "No" that follow. "Yes" means you want to be told. "No" means you do not want to be told. Please place a check and initial your preference.

Please mark a check in the appropriate box.

☐ Yes ☐ No _____ initials

If you choose not to be told no other informative action will be taken. However if you choose to be informed and information about you is discovered, a letter asking you to make an appointment with the researchers will be sent to your home. During this appointment, you will be informed of the findings and offered counseling/education on the subject.

SAMPLE DONATION: During this study, you will be asked to provide blood samples. These samples will be used for isolation of DNA(deoxyribonucleic acid – carrier of genetic information in the cells), RNA (ribonucleic acid – transmits genetic information from DNA in the cells), and proteins for analysis, and for the establishment of cell lines (specific cells maintained outside of a living person for research and/or medical purposes), and may also be used for purposes that are currently unknown. There is a chance that the samples that you are donating under this study may be used in other research studies and may have some commercial value. Should your donated sample(s) lead to the development of a commercial product, the institution(s) (The Coriell Institute for Medical Research) or inventor(s) who developed the product will own it and may take action to patent and license the product. The Institute does not intend to provide you with any compensation for your participation in this study nor for any future value that the sample you have given may be found to have. You will not receive any notice of future uses of your sample(s). You are being asked to make the choice in this form by checking the box the "Yes" or "No" that follow. "Yes" means you agree to allow any sample(s) collected for this study to be used for further research. "No" means you do NOT want your sample(s) to be used for any further research other than this study.

Please mark a check in the appropriate box.

☐ Yes ☐ No _____ initials

Subject Initials: _____

Date: _____

Thomas Jefferson University
Raffaello Baffa, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #05C.36
DOD/Cornell Institute
Page 4 of 8

Risks/Discomforts

The risk of discovering that you have a genetic predisposition to cancer will be discussed with you prior to agreeing to participate in the study. This may cause you concern. You may also have concerns even if you are not in the future told that you have a gene alteration that has been linked to an increased risk of prostate cancer. You do not have to agree to have this information revealed to you or your family members. Some people are concerned about genetic discrimination by insurance companies and/or employers. We will not release any information about you or your family to an insurance company or employer without your consent. The risks and discomfort associated with giving blood include the possibility of bleeding and bruising. This rarely causes a severe problem.

You should call the study doctor immediately if, during the course of this study, any of these side effects (or symptoms) develop. The study doctor has told you that should your condition worsen, should side effects become very severe, or should new scientific developments occur that indicate that this treatment is not in your best interest, your participation in the study will be stopped.

Alternatives To Participation

Your alternative is not to participate in this study.

Confidentiality

You have rights regarding the privacy of your medical information collected prior to and in the course of this research. This medical information, called "protected health information" (PHI), includes demographic information (e.g., your name, address, etc.), certain aspects of your medical history, the results of physical exams, blood tests, x-rays and other diagnostic and medical procedures conducted in the course of the research. You have the right to limit the use and sharing of your PHI, and you have the right to see your research study records and know who else is seeing them.

While the research is in progress, you will not be allowed to see your health information that is created or collected during the course of the research. After the research is finished, however, you may see this information.

By signing this consent form, you are allowing the research team to have access to your PHI. The research team includes the investigators listed on this consent form and other personnel involved in this specific study. Your PHI will also be shared, as necessary, with the University's Division of Human Subjects Protections and the Institutional Review Board (a University committee that reviews, approves and monitors research involving human subjects). All of these people and entities are obligated to protect your PHI.

Subject Initials: _____
Date: _____

Thomas Jefferson University
Raffaele Beffa, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #05C.36
DOH/Coriell Institute
Page 5 of 8

You are also allowing the research team to share your PHI with other people or groups specified below:

- Employees of Thomas Jefferson University involved in the conduct of this study
- Employees of Thomas Jefferson University Hospital involved in the conduct of this study
- Employees of the Coriell Institute of Medical Research involved in the conduct of this study

All of the above entities are obligated to protect your PHI.

The Department of Defense, which sponsors this research collaboratively with the Coriell Institute for Medical Research, and is providing funds to Thomas Jefferson University to conduct

this research, and its representatives will ensure that study activities are being performed properly and that study data are being recorded accurately. Although these entities may have their own confidentiality procedures to protect your PHI, they are not covered by the same federal privacy rule (the Health Insurance Portability and Accountability Act of 1996, or HIPAA) that governs the healthcare industry, and therefore are not bound to its regulations.

The PHI that may be used or disclosed and the purposes for those uses or disclosures are as follows:

Demographic Data: name, address, telephone number, date of birth, social security number, sex, ethnic group, medical record number. The demographic data allows us to identify you, the patient.

Study Data for Analysis: chart progress notes taken during your participation in the study. You will be asked to provide your history of the disease, medical history, current and previous treatments taken, and information on associated diseases. Also dates of participation in study, dates of study visits and telephone contacts. Other data will include laboratory reports (blood tests and urine tests), pathology reports, and information regarding your health status during and after completing treatment (as it relates to the study). Other information collected by questionnaire will include reproductive and sexual history, health behaviors such as cigarette smoking and alcohol use, dietary intake, and family history of cancer and clinical characteristics of these individuals.

Other: If you develop an illness or injury in the course of your participation in this study, other PHI about treating and following your condition may be generated.

Subject Initials: _____

Date: _____

Thomas Jefferson University
Raffaele Baffa, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #05C36
DOD/Coriell Institute
Page 6 of 8

Information gathered as part of your participation in this research study will be recorded from your study records. Your study doctor will disclose this information to the study sponsor, and the information may be maintained indefinitely in their files.

Your name or other personal identifiers will not appear on any forms sent to the sponsor or to the Coriell Institute. Instead, you will be assigned a patient identification number. The research doctor will keep a list that matches patient identification numbers to patient names, but the list will not be sent to the sponsor. Also, this form will be kept with your research file at the study site for review, but will not be sent to the sponsor.

If you do not sign this consent form, you will be ineligible to participate in the research study for which this consent is being requested.

You are authorizing us to use and disclose your PHI indefinitely.

You may revoke this authorization to use and share your PHI at any time by contacting the principal investigator, in writing, at Dr. Raffaele Baffa, 1025 Walnut Street, Suite 1100, Philadelphia, PA 19107.

Dr. David Moscatello is located at the The Coriell Institute for Medical Research at 403 Haddon Avenue in Camden, NJ, 08103. More information on Dr. Moscatello and Coriell can be found at their website at <http://www.coriell.org/> or by writing to the Institute.

If you revoke this authorization, you will no longer be able to participate in this research study, and the use or sharing of future PHI will be stopped. However, the PHI that has already been collected may still be used.

The results of clinical tests and therapy performed as part of this research may be included in your medical records. The information from this study may be published in scientific journals or presented at scientific meetings but you will not be personally identified in these publications and presentations.

Compensation in the Case of Injury

In the event that you experience a research-related injury, comprehensive medical and/or surgical ☐ (including hospitalization) to the extent needed and available will be provided. However, Thomas Jefferson University cannot assure that this comprehensive medical and/or surgical care will be provided without charge, and the costs incurred for this care may ultimately be your responsibility. A research-related injury is a physical injury or illness resulting to you as a direct result of the experiments, treatment(s) and/or procedure(s) used in this study that are different from the medical treatment you would have received if you had not participated in this study. No other financial compensation is available.

Subject Initials: _____

Date: _____

Thomas Jefferson University
Raffaele Baffa, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #05C-36
DOD/Coriell Institute
Page 7 of 8

Benefit to Subject

Although you will receive no immediate benefit from your participation in the study, investigators hope that the knowledge gained from future research studies will be of benefit to you, your relatives, and future generations.

Payment

You will not receive payment for your participation in this study.

Contact Information

If you have any questions or concerns about this research, or if you experience a research-related injury, call the Principal Investigator, Dr. Raffaele Baffa at Telephone: 215-955-6961. Should you have any questions regarding your rights as a research participant, you may contact Thomas Jefferson University's Institutional Review Board, which is concerned with the protection of participants in research studies, at Telephone: (215) 503-8966.

Significant New Findings

As the research progresses, any significant new finding(s), beneficial or otherwise, will be told to you and explained as they relate to the course of your treatment.

Disclosure of Financial Interest

The sponsor of this study, the Department of Defense and the Coriell Institute for Medical Research, is paying Thomas Jefferson University to conduct this study.

VOLUNTARY CONSENT AND SUBJECT WITHDRAWAL

You voluntarily consent to participate in this research investigation. You have been told what your participation will involve, including the possible risks and benefits.

You may refuse to participate in this investigation or withdraw your consent and discontinue participation in this study without penalty and without affecting your future care or your ability to receive medical treatment at Thomas Jefferson University.

In the event that you withdraw from the study, the study doctor will ask your permission to continue study follow-up, and all clinical data, as it relates to the study, will continue to be collected from your medical records.

Subject Initials: _____
Date: _____

02/02/2006 11:31 2159231884

TJU UROLOGY

PAGE 10/11

Thomas Jefferson University
Raffaella Batta, MD
Genetic Factors for Prostate Cancer
215-955-6961
IRB Control #03C.36
DOD/Coriell Institute
Page 2 of 8

Non-Waiver of Legal Rights Statement

By your agreement to participate in this study, and by signing this consent form, you are not waiving any of your legal rights.

My signature below indicates that I have read and understood all the information given to me in this document. The information in this document has been explained to me and I have had the opportunity to ask questions. My signature below indicates that I voluntarily agree to participate in the study described in this document.

Signatures:

Your Name (please print or type) (Date)

Signature of Next of Kin /Patient's Surrogate (Date)

Your Signature (Date)

Name of Person Conducting Consent Interview (Date)

Signature of Person Conducting Consent Interview (Date)

Signature of Principal Investigator or
Co-Investigator (Date)

Do Not Write Below This Line

For IRB Stamping

As per University Counsel - Do not sign

this consent form after 1-9-07

02/02/2006 11:31 2159231884

TJU UROLOGY

PAGE 11/11

For office use only	
ID #	
MR #	
Initial Visit	/ /
	MM DD YY

Health History Questionnaire
Family Risk Assessment for Prostate Cancer
Minimal Data Set

This questionnaire has been developed to collect information about your family history and your personal health. This information will help us identify medical or family history information that is important in understanding cancers that may run in a family. Participation is voluntary and you can withdraw at any time. All the information that you provide will be kept confidential. A code number will be used to track any information and your name will not be used. Thank you for your participation.

1. How old are you? _____
2. State of birth _____
3. If not US. born, number of years living in the U.S. _____
4. In what country or state have you lived most of your life? _____
5. What is the highest level of education you have completed?
 - 1 ☐ Less than 8 years
 - 2 ☐ 8 to 11 Years (without graduation)
 - 3 ☐ High School graduation/G.E.D.
 - 4 ☐ Vocational or technical school
 - 5 ☐ Some college or university
 - 6 ☐ Bachelor's degree
 - 7 ☐ Graduate degree

6. Are you currently:

Thomas Jefferson University IRB
Approval Date 1-10-06
Expiration Date 1-9-07
Annual review due 6 weeks before expiration.

EXHIBIT D

• Page 1

March 7, 2005

December 11, 2003

Mr. Archie B. Cardwell

Grants/Contract Specialist

United States Army Medical Research Acquisitions Activity

ATTN: MCMR-RMI-S
504 Scott Street
Fort Detrick, MD 21702-5014

Re: Award Number DAMD17-01-1-0080
"Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat polymorphisms in African-American and Caucasian males: Influence on Prostate Cancer risk or disease progression and interaction with Androgen receptor CAG repeat polymorphisms."

Dear Mr. Cardwell,

I was authorized to initiate my research by the Human Subjects Protection reviewers in the Office of Regulatory Compliance and Quality on authorized [CAN YOU GIVE THE DATE]. Because the initial performance period for the award was 1 September 2001, the research was originally scheduled to be completed by 31 August 2004. However, due to the long delay in obtaining the HSRRB approval, I am only now able to begin the research. I am therefore requesting an extension of the grant to August 31, 2006, in accordance with the proposed research plan of three (3) years.

In light of the delay that was completely out of my control, look forward to your favorable consideration of this request.

Sincerely,

David K. Moscatello, Ph.D.
Assistant Professor and Supervisor,
Differentiated Cell Laboratory

Coriell Institute for Medical Research
403 Haddon Avenue
Camden, New Jersey 08103-1505
Phone (856) 966-5054
FAX: (856) 964-0254
E-mail: dmoscate@coriell.umdnj.edu

cc: Nrusingha C. Mishra, Ph.D.

Cardwell, Archie B Mr USAMRAA, 12/12/03 8:23 AM -0500, RE: Award Number DAMD

EXHIBIT F

Date: Fri, 12 Dec 2003 08:23:43 -0500
 From: "Cardwell, Archie B, Mr USAMRAA" <archie.cardwell@us.army.mil>
 Subject: RE: Award Number DAMD17-01-1-0080
 To: "David K. Moscatello" <dmoscate@coriell.umdj.edu>,
 "Cardwell, Archie B Mr USAMRAA" <archie.cardwell@us.army.mil>
 Cc: "Mishra, Nrusingha C Dr USAMRMC" <nrusingha.mishra@us.army.mil>,
 David Beck <dbeck@coriell.umdj.edu>,
 "Joseph L. Mintzer" <jmintzer@coriell.umdj.edu>
 MIME-version: 1.0
 Status:

Dr. Moscatello,

Dr. Mishra and I have discussed your request and we have decided to honor it, however we feel one year extension would be more appropriate at this time in order to gauge your progress. I will execute a Modification extending your assistance agreement through 09/30/2005 for the time being.

Feel free to call me if you have any questions.

Archie B. Cardwell Jr.
 Grant/Contract Specialist
 USAMRAA
 BLDG 820, Chandler Street
 Fort Detrick, MD 21702
 301-619-2630
 FAX: 301-619-3002
 archie.cardwell@amedd.army.mil

-----Original Message-----

From: David K. Moscatello <dmoscate@coriell.umdj.edu>
 Sent: Thursday, December 11, 2003 3:06 PM
 To: Cardwell, Archie B Mr USAMRAA
 Cc: Nrusingha C. Mishra, Ph.D.; David Beck; Joseph L. Mintzer
 Subject: RE: Award Number DAMD17-01-1-0080

December 11, 2003
 Mr. Archie B. Cardwell
 Grants/Contract Specialist
 United States Army Medical Research Acquisitions Activity

ATTN: MCMR-RMI-S
 504 Scott Street
 Fort Detrick, MD 21702-5014

RE: Award Number DAMD17-01-1-0080. Epidermal Growth Factor (EGF) Receptor intron 1 CA repeat polymorphisms in African-American and Caucasian males: Influence on Prostate Cancer risk or disease progression and interaction with Androgen receptor CAG repeat polymorphisms.

Dear Mr. Cardwell,

I was authorized to initiate my research by the Human Subjects Protection reviewers in the Office of Regulatory Compliance and Quality in a letter dated 24 November, 2003. Because the initial performance period for the award was 1 September 2001, the research was originally scheduled to be completed by 31 August 2004. However, due to the long delay in obtaining the HSRB approval, I am only now able to begin the research. I am therefore requesting an extension of the grant to August 31, 2006, in accordance with the proposed research plan of three (3) years.

In light of the delay that was out of my control, I look forward to your favorable consideration of this request.

Printed for "David K. Moscatello" <dmoscate@coriell.umdj.edu>